

# **EXHIBIT 171**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration

Central Region  
New Jersey District

November 9, 2007

North Brunswick Resident Post  
120 North Center Drive  
North Brunswick, NJ 08902  
(732) 940-8996

Apurva Patel, Managing Director  
Actavis Totowa, LLC  
101 East Main Street  
Little Falls, New Jersey 07424

Dear Mr. Patel:

We are enclosing a copy of the establishment inspection report (EIR) for the inspection conducted at your premises at 101 East Main Street, Little Falls, New Jersey on September 5, 2007 et al. behalf of the U.S. Food and Drug Administration (FDA). This report is being provided to you for information purposes.

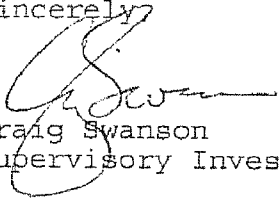
This new procedure is applicable to EIRs for inspections completed on or after April 1, 1997. For those inspections completed prior to the above date, a copy of the EIR may still be made available through the Freedom of Information Act (FOIA).

The Agency is working to make its regulatory process and activities more transparent to the regulated industry. Releasing this EIR to you is part of this effort. The copy being provided to you comprises the narrative portion of the report; it reflects redactions made by the Agency in accordance with the FOIA and 21 C.F.R. Part 20. This, however, does not preclude you from requesting and, possibly, obtaining any additional information under FOIA.

If there is any question about the released information, feel free to contact Richard Manney at (973) 331-4902 or write to:

U.S. Food and Drug Administration  
10 Waterview Blvd.  
Parsippany, New Jersey 07054

Sincerely,

  
Craig Swanson  
Supervisory Investigator



**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI:

2244683


EI Start:

09/05/2007

EI End:

09/28/2007

## TABLE OF CONTENTS

SUMMARY.....	2
ADMINISTRATIVE DATA .....	2
HISTORY .....	4
COMPLIANCE STATUS .....	5
INTERSTATE COMMERCE .....	5
JURISDICTION .....	5
INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED .....	5
CHANGES IN OPERATIONS AND PERSONNEL.....	7
FIRM'S TRAINING PROGRAM .....	10
MANUFACTURING OPERATIONS.....	10
MANUFACTURING CODES .....	10
COMPLAINTS .....	11
INSPECTIONAL COVERAGE .....	11
	
RECALL .....	14
MARKET WITHDRAWAL.....	15
BLEND UNIFORMITY .....	15
QUALITY SYSTEM.....	16
FACILITIES AND EQUIPMENT SYSTEM.....	16
MATERIALS SYSTEM.....	16
PRODUCTION SYSTEM.....	16
LABORATORY CONTROL SYSTEM .....	17
OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE.....	17
REFUSALS.....	22
GENERAL DISCUSSION WITH MANAGEMENT .....	22
SAMPLES COLLECTED .....	24
VOLUNTARY CORRECTIONS.....	25
EXHIBITS COLLECTED .....	38
ATTACHMENTS.....	39

**Establishment Inspection Report**

Actavis Totowa LLC  
 Little Falls, NJ 07424-5608

FEL: 2244683  
 EI Start: 09/05/2007  
 EI End: 09/28/2007

**SUMMARY**

This inspection of a pharmaceutical manufacturer was conducted as a follow-up to Warning Letter # 07-NWJ-06 and was completed as part of the NWJ-DO FY07 Drug Work Plan under FACTS Assignment # 4041339, Operation ID # 3240435. The inspection provided general GMP coverage as well as pre-approval coverage of ANDA 40830/000 Acetaminophen, Caffeine, and Dihydrocodeine Bitartrate Capsules 356.4 mg / 30 mg / 16 mg. Inspectional guidance was afforded through Compliance Program Guidance Manuals 7356.002: Drug Manufacturing Inspection and 7346.832: Pre-Approval Inspections/Investigations.

The previous GMP inspection of 7/10/2006 et. al., provided coverage to the Quality, Production, Laboratory Control and Materials Systems. Limited coverage was also provided to the Facilities & Equipment System as necessary, but this system was not covered in its entirety. An FDA 483, Inspectional Observations, was issued at the closeout meeting regarding deficiencies in the areas of Quality Control, laboratory records, OOS and production investigations, cleaning validation, bulk stability testing, detection and documentation of OOS results, sampling documentation, equipment qualification, calibrations and preventive maintenance, rejected materials and storage of components. In addition, a discussion was held with management regarding the labeling of laboratory glassware and stability of solutions. Corrections were promised for all observations and discussion items. The inspection was classified OAI for GMP deficiencies and Warning Letter # 07-NWJ-06 was issued.

The Quality, Production, Laboratory Control, Materials and Facilities & Equipment Systems were covered during the current inspection and corrections made since the previous inspection were verified. An FDA 483, Inspectional Observations, was issued at the closeout meeting regarding deficiencies in the areas of Field Alerts, the stability testing program, and investigations. In addition, a discussion was held with management regarding additional items not listed on the FDA 483. Corrections were promised for all observations and discussion items. An approval recommendation was submitted for [REDACTED]

[REDACTED] mg upon completion of the inspection. Corrections to the previous PADE inspection will be verified under the next assignment for the Elizabeth facility as all ADE operations have been transferred to that facility since the previous inspection.

**ADMINISTRATIVE DATA**

Inspected firm: Actavis Totowa LLC  
 Location: 101 E Main St  
 Little Falls, NJ 07424-5608

**Establishment Inspection Report**

Actavis Totowa LLC  
 Little Falls, NJ 07424-5608

FEI: 2244683  
 EI Start: 09/05/2007  
 EI End: 09/28/2007

Phone: 973-890-1440  
 FAX:  
 Mailing address: 101 E Main St  
 Little Falls, NJ 07424-5608

Dates of inspection: 9/5/2007, 9/6/2007, 9/10/2007, 9/11/2007, 9/12/2007, 9/13/2007,  
 9/14/2007, 9/18/2007, 9/20/2007, 9/21/2007, 9/24/2007, 9/25/2007,  
 9/26/2007, 9/27/2007, 9/28/2007

Days in the facility: 15

Participants: Kristy A. Zielny, Investigator

On 9/5/07, I, Investigator Kristy A. Zielny, presented my credentials and issued an FDA 482, Notice of Inspection, to Mr. Apurva Patel, Managing Director. Mr. Patel stated he was authorized to receive the Notice. A "Resources for FDA Regulated Businesses" form was also presented at this time. I explained that the purpose of my visit was to provide follow-up coverage to Warning Letter # 07-NWJ-06, pre-approval inspectional coverage to [REDACTED] as well as GMP inspectional coverage. Mr. Jasmine Shah, Vice President, Regulatory and Medical Affairs, was also present for the initiation of the inspection. Mr. Scott Talbot, Site Head of Quality joined the inspection later that morning.

Mr. Scott Talbot provided all requested information and documentation as requested and arranged meetings with additional personnel as necessary. A facility tour was also provided.

[REDACTED]

On 9/28/07, an FDA 483, Inspectional Observations, was issued to Mr. Apurva Patel, Managing Director. In addition, a discussion was held with management both during the inspection and again at the closeout meeting. Corrections were promised for all observations and discussion items. A written response to the 483 observations was promised as well.

A recommendation of approval was submitted for ANDA 40830/000 [REDACTED] upon the close of this inspection.

[REDACTED]

**Establishment Inspection Report**

Actavis Totowa LLC  
 Little Falls, NJ 07424-5608

FEI: 2244683  
 EI Start: 09/05/2007  
 EI End: 09/28/2007

**HISTORY**

Actavis Totowa LLC currently consists of three sites. This site, located at 101 East Main Street, Little Falls, NJ, is responsible for all manufacturing and testing as well as raw material receiving. The second site is located at 4 Taft Road, Totowa, NJ, and is responsible for all packaging, labeling, distribution, packaging component receiving and R&D. Some overflow testing is also completed at the Taft Road Facility as well as the testing of ANDA submission batches. Actavis Totowa LLC is in the process of moving its operations from the Little Falls facility to a third site, located at 900 Riverview Drive, Totowa, NJ. The Riverview facility is listed under the same FEI # as the Little Falls site and is currently being used for storage and office space. Laboratory equipment has already been transferred to the Riverview site and the Quality Control Laboratory is expected to initiate testing any day. All operations currently at the Little Falls facility are expected to be fully transferred to the Riverview site. The Riverview facility was visited as part of the current inspection.

This site, previously operating as Amide Pharmaceutical, Inc. was founded in 1983 and was acquired by Actavis on July 27, 2005. The name legally changed to Actavis Totowa LLC on May 15, 2006. Actavis Totowa LLC is a wholly owned subsidiary of Actavis Group, which was founded in 1956 and is based in Reykjavick, Iceland.

All regulatory correspondence should be addressed to Mr. Apurva Patel, Managing Director of Actavis Totowa LLC, at 101 East Main Street, Little Falls, NJ 07424. Mr. Apurva Patel is the most responsible individual at this facility, which is also the current headquarters for Actavis Totowa LLC. Mr. Divya Patel, President of Actavis U.S. Operations should also be copied on all correspondence at 900 Riverview Drive, Totowa, NJ.

This facility currently operates 7:30 AM through 4:00 PM, Monday through Friday, and as needed on weekends. There are approximately 125 individuals employed at this facility. This site consists of two buildings: Building A is 40,000 square feet and consists of administration, manufacturing, QA, QC, RA, and warehouse. Building B is approximately 20,000 square feet and is being decommissioned but is still used for some warehousing operations. The floor plan of the manufacturing facility at Little Falls is attached as **Exhibit 1**. The Riverview facility, where operations are slated to be transferred, consists of nearly twice as much space with 106,000 square feet, 41,000 of which will be manufacturing space.

[REDACTED]

The annual volume of sale for Actavis Totowa LLC, was approximately \$160 million in 2006.

**Establishment Inspection Report**

Actavis Totowa LLC  
Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

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**COMPLIANCE STATUS**

A Warning Letter was issued to Actavis Totowa LLC, Little Falls, as a result of the previous inspection. The firm has been operating under a Compliance Hold since the receipt of Warning Letter # 07-NWJ-06.

A second Warning Letter was issued to Actavis Totowa LLC, Little Falls, on 2/26/07 for the manufacturing of DESI products. The production of all of these products has been discontinued.

**INTERSTATE COMMERCE**

Mr. Scott Talbot provided an estimation of interstate commerce at approximately 85 to 90%. Products that are manufactured at 101 East Main Street, Little Falls, are packaged, labeled at the 4 Taft Road, Totowa facility before being sent to UPS for distribution. All products are sent to UPS Louisville located at 1860 Outerloop, Louisville, KY 40219, with the exception of controlled substances, which are sent to UPS Newark, 222 Lake Drive, Newark, DE 19702. The Central Distribution Center is no longer being used for distribution functions.

**JURISDICTION**

Actavis Totowa LLC is a large generic pharmaceutical manufacturer. The Little Falls facility is responsible for raw material receiving, all manufacturing and testing of drug products. Dosage forms manufactured at this facility include prompt release tablets and capsules and extended release tablets. A complete list of products manufactured at the Little Falls facility was provided and is attached as **Exhibit 2**.

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**INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED**

Mr. Scott Talbot accompanied me throughout the inspection and arranged for meetings with additional individuals as necessary. Individuals who provided information throughout the inspection include the following:

Scott Talbot, Site Head of Quality

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

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Apurva Patel, Director, Site Operations

Phyllis Lambridis, VP, Quality Compliance for Actavis U.S.

Jasmine Shah, VP, Regulatory and Medical Affairs for Actavis, U.S.

Wanda Eng, Sr. Director Corporate Compliance for Actavis U.S.

Daniel Bitler, Director, QA Director – Little Falls

Richard Dowling, Director, Manufacturing Operations

Garret Wolan, Compliance Manager for Actavis U.S.

Nilesh Patel, QC Instrument &amp; Metrology Manager

Elina Novikov, QC Laboratory Compliance Manager

Gaurang Pandya, Group Leader, Analytical Research

Katherine Chuang, Project Manager

Vince D'Esposito, Training Manager

Bernard Glover, QA Specialist

The following are the key officials of Actavis Totowa LLC:

Mr. Apurva Patel, Director, Site Operations

Mr. Patel is responsible for leading all site activities and is accountable for Manufacturing, Health & Safety, Release, Engineering and Maintenance. Mr. Patel reports to Mr. Steinthor Palsson, EVP Operation, Management Board, who, in turn reports directly to Mr. Robert Wessman, CEO.

Mr. Scott Talbot, Site Head of Quality

Mr. Talbot is responsible for the assurance of quality within Actavis Totowa, LLC. He is responsible for all Quality Systems as they relate to the development, manufacturing testing and distribution of pharmaceutical products under GMPs. Mr. Talbot reports to Mr. Divya Patel, Executive Chairman, Management Board, who, in turn reports directly to Mr. Robert Wessman, CEO.

Mr. Daniel Bitler, QA Director – Little Falls

Mr. Bitler is responsible for the assurance of quality within the Little Falls sites. He is responsible for all Quality Systems as they relate to the manufacturing and distribution of pharmaceutical products manufactured at the Little Falls facilities.

Mr. Swapan Roychowdhury, Quality Control Director

Mr. Roychowdhury is responsible for all Quality Control functions. He is responsible for all testing of all raw materials and finished products as well as the training of analysts, the evaluation of data and the assurance that all instruments are qualified, calibrated and maintained.

**Establishment Inspection Report**

Actavis Totowa LLC  
 Little Falls, NJ 07424-5608

FEL: 2244683  
 EI Start: 09/05/2007  
 EI End: 09/28/2007

Mr. Anthony Castellazzo, QS Director – Totowa

Mr. Castellazzo is responsible for the assurance of quality within the Totowa sites. He responsible for Validation, Technology Transfer and the packaging and distribution of pharmaceutical products from the Totowa sites. He is also responsible for assuring all equipment, facilities, utilities and processes are validated.

Mr. Paul Galea, QS Director

Mr. Galea is responsible for all Internal Audits, Complaints, Change Control, CAPA and Training.

Mr. Harish Vakil, Validation Associate Director

Mr. Vakil is responsible for the validation of all facilities, utilities, equipment, processes and cleaning related to the manufacturing, packaging, and distribution of pharmaceutical products.

Mr. Richard Dowling, Director of Manufacturing Operations

Mr. Dowling is responsible for all manufacturing operations related to all Actavis Totowa LLC products.

Mr. Bharat Patel, Vice President, Materials Management

Mr. Bharat Patel is responsible for all purchasing for the Actavis Totowa facilities as well as production planning and managing inventory.

Organizational charts and Position Descriptions were provided and are attached as **Exhibits 3 and 4**, respectively.

The most responsible individual at this site is Mr. Apurva Patel, Director, Site Operations. All regulatory correspondence should be addressed to his attention at 101 East Main Street, Little Falls, NJ 07424.

#### **CHANGES IN OPERATIONS AND PERSONNEL**

The following changes in personnel have taken place since the previous inspection of January 2006.

Mr. Apurva Patel, previously Director, Project Management, became Site Head of Operations as of June 2007.

Mr. Scott Talbot, Site Head of Quality, came to Actavis Totowa LLC as of 1/9/07.

Mr. Anthony Castellazzo became Director, Quality Assurance – Totowa as of July 2007

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

Mr. Swapan Roychowdhury became Director, Quality Control as of April 2007.

Mr. Harish Vakil, Acting Director, Validation came to Little Falls as of May 2007.

Mr. Paul Galea became Director, Quality Systems as of May 2007.

Mr. Steinthor Palsson, previously Site head of Operations, Malta, became Executive VP, Operations as of August 2006.

Mr. Divya Patel, previously President and CEO of Actavis Totowa LLC, became Executive Chairman as of April 2007.

Mr. Jasmine Shah, previously VP, Regulatory and Quality Compliance, became VP, Regulatory and Medical Affairs as of January 2007.

Ms. Phylis Lambridis, joined Actavis as Vice President of Quality and Compliance, U.S. in September 2007.

A number of additional individuals have been hired and/or have been promoted since the previous inspection, including, but not limited to:

Vince D'Esposito, Training Manager

Jisheng Zhu, Quality Control Manager

Elina Novikov, Stability Manager

Chrystal Day, Stability Coordinator

Joaquin Mejia, Stability Coordinator

Bernard Glover, CAPA and Complaints Specialist

Mike Ponzo, Investigation Specialist

Elizabeth Guarch, Validation Manager

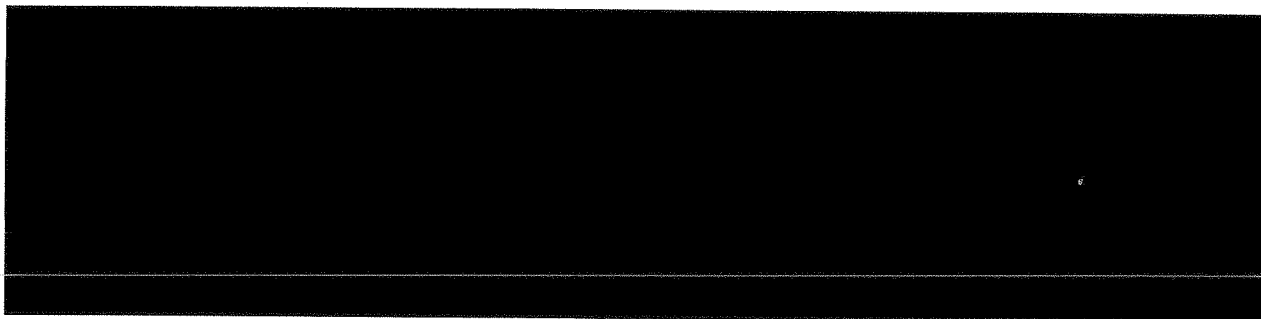
Irina Kotkova, Validation Specialist

Lauren Miranda, Quality specialist

Pam Barckett, Documentation Specialist

In addition, four new analysts and two temps have been brought into the QC Laboratory. An additional two analysts were hired during the course of the inspection.

The following changes have been made in operations since the previous inspection:



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**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

The reporting of Adverse Drug Events has been moved to the Elizabeth facility as of April 2006.

The Quality Systems Improvement Plan (QSIP) was initiated as of August 29, 2006. QSIP was organized into 17 sections, including Organization, Management Review, Laboratory Controls, Micro/Environmental Monitoring, Investigations, CAPA, Documentation, Change Control, Validation, Training, Incoming Materials, Finished Product Release, Compliance/Audits, Warehouse/Distribution, Facilities and Equipment, Manufacturing Technology Transfer and Computer Validation. A copy of the plan was provided and is attached as **Exhibit 6**. Consultants were utilized beginning in September 2006 in order to assess key areas.

All Standard Operating Procedures (SOPs) and Departmental Operating Instructions (DOIs) have been reviewed and uploaded into QMAS, a validated computer system, which will enable employees to access all procedures and instructions on-line and will ensure that only the most current revision of each SOP and DOI is available for reference. Laboratory methods are currently being entered into the QMAS system for the same purpose.

Calibration Manager (CALMAN) was validated in the end of 2006. This program has been fully operational since March 2007 and is used for the scheduling and documenting of calibration and preventative maintenance operations in both the laboratory and manufacturing.

Microcontrol Solutions Stability System II has been implemented in order to manage the stability program. The software generates pull schedules and is used for storing all information related to the stability program.

Trackwise is to be utilized in the future in order to document and track Deviations, Investigations, Change Controls, Out of Specification Investigations. The roll-out of this program is anticipated to be by the end of 2007.

TM2000 will be utilized for tracking all training operations.

JD Edwards –Inventory System will be rolled out in the next 6 months, which will control the inventory of raw materials, bulk product and finished products.

Manufacturing Operations are going to be moved over to the Riverview facility. The first products that will be scheduled for production at the Riverview site will be some of the vitamin products, followed by Digoxin as well as other dry blend products. The Quality Control Laboratory is also set to begin testing and analysts started moving over to the Riverview facility during the course of the current inspection. The QC Laboratory is going to be using Empower Software for their Data Acquisition System for running the HPLCs and will move away from using the TotalChrom System.

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

The Central Distribution Center is no longer being used for all distribution functions. These functions were transferred to UPS as of March and April 2007.

**FIRM'S TRAINING PROGRAM**

Since the previous inspection Mr. Vincent D'Esposito, QA Manager, Training has joined Actavis Totowa, LLC. Mr. D'Esposito is responsible for managing the training program, which includes GMP, SOP and OJT training. He is also responsible for maintaining all training records. The training program includes initial GMP training to be given during the first week of employment as well as ongoing GMP training.

**MANUFACTURING OPERATIONS**

Actavis Totowa LLC, Little Falls is a large generic pharmaceutical manufacturer. This facility continues to be responsible for raw material receiving, all manufacturing and testing of drug products. Dosage forms manufactured at this facility include prompt release tablets and capsules and extended release tablets. A complete list of products manufactured at the Little Falls facility was provided and is attached as **Exhibit 2**.

**MANUFACTURING CODES**

Manufacturing codes were explained to be assigned as follows:

The first digit indicates the year of production (7 = 2007). The following four digits are a consecutive number representing the number Batch produced in that year (0001 would indicate this was the 1st Batch manufactured in that particular year). The following character is a letter indicating if the Batch was divided by different logos or customers ("A" would indicate the first logo or customer and "B" would indicate the second). The last digit would be indicative of the packaging configuration ("1" would represent the first packaging configuration and "2" would indicate the second).

**Establishment Inspection Report**

Actavis Totowa LLC  
Little Falls, NJ 07424-5608

FEI: 2244683  
EI Start: 09/05/2007  
EI End: 09/28/2007

**COMPLAINTS**

Complaints were reviewed during this inspection. A discussion was held regarding the length of time taken to close complaints. Complaints received in the last three months have been handled in a timely manner. (Please see Discussion with Management Section of this report for additional details.)

**INSPECTIONAL COVERAGE**

The Quality, Production, Laboratory Control, Materials and Facilities & Equipment Systems were covered during the current inspection and corrections made since the previous inspection were verified. Pre-approval coverage was also provided to ANDA 40830/000 [REDACTED]

Items reviewed during this inspection include, but were not limited to:

**Facility Tour**  
[REDACTED]

Development Report

Regulatory Correspondence

Standard Operating Procedures (SOPs)

Receiving and Warehousing Procedures

Equipment Cleaning and Usage Logs

Equipment Calibration and Preventive Maintenance

Analytical Raw Data (raw material, finished product, stability)

Batch Records (masters and executed)

OOS Investigations

Production Investigations

Rejected Batches

Recall: Dantrolene 25 mg Capsules  
[REDACTED]

Materials in Quarantine

Deviations and Investigations

Change Controls

Complaints

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

GMP Training

Equipment Qualifications

Cleaning Validations

Recovery Studies

Process Validations

Annual Product Reviews

Method Validations

Stability Data

Laboratory Notebooks

TotalChrom Data Acquisition System

Pest Control

Bin Cards

Micro Control Solutions Stability Systems II

QSIP

Corrections to previous FDA 483

**ANDA 40830/000 ACETAMINOPHEN, CAFFEINE, AND DIHYDROCODEINE  
BITARTRATE CAPSULES 356.4 MG / 30 MG / 16 MG**



The CMC section of the application was reviewed as well as the development report, specifications for raw materials and finished product, raw analytical data for raw materials, in-process samples, finished product, and stability samples, method validations, revisions to methods, reference standards, the executed Batch record, equipment qualifications, calibrations and preventive maintenance, and cleaning logs. A flow diagram of the manufacturing process was provided and is attached as (Exhibit 7).

All in-process and finished product testing was performed at the Taft Road Facility. This data was reviewed at the Taft Road facility as part of this inspection.

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEL: 2244683

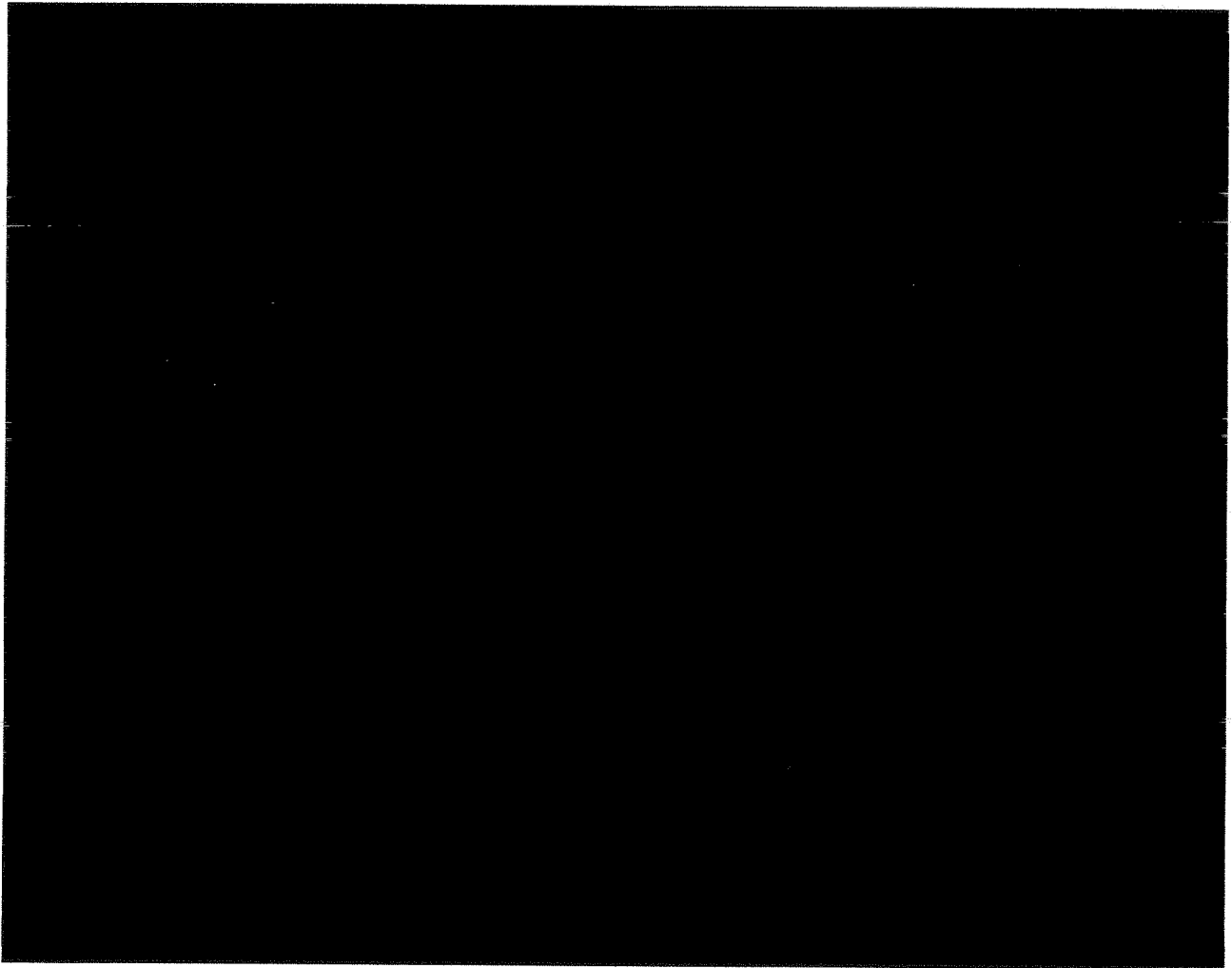
EI Start: 09/05/2007

EI End: 09/28/2007

Micro testing is contracted out to Gibraltar laboratories, 122 Fairfield Road, Fairfield, NJ 07004 and Celsis laboratories, 165 Fieldcrest Avenue, Edison, NJ 08837



**FIELD ALERT:**  
**LOT # 60484A1**



**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FBI: 2244683

EI Start: 09/05/2007

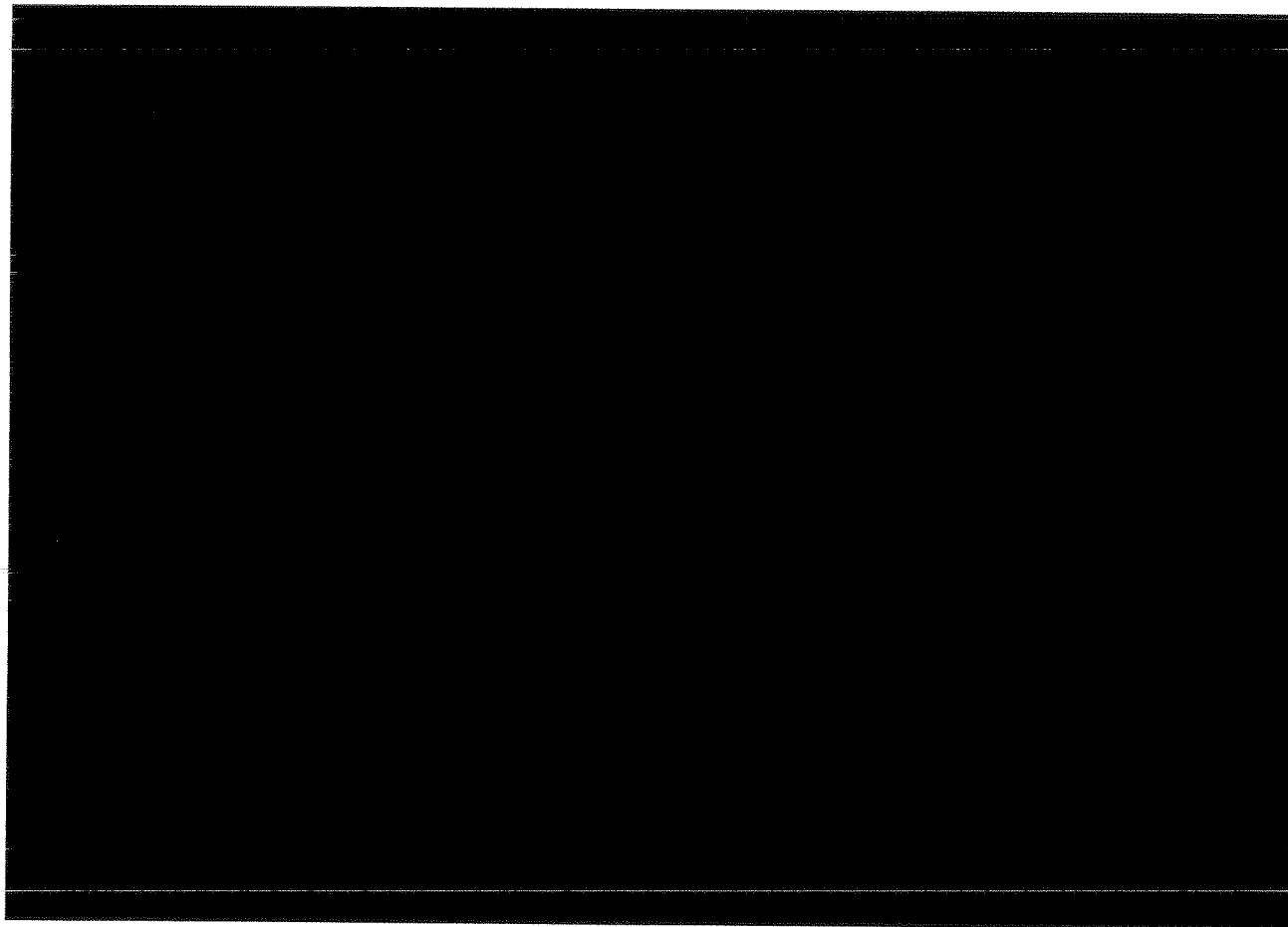
EI End: 09/28/2007

I indicated that there were long gaps between the original testing on 8/21/07 and the repeat test performed on 8/28/07 and again between 8/28/07 and 9/7/07. Mr. Talbot explained that this was an error made in scheduling when the Laboratory Supervisor was on vacation. He indicated that the testing that actually occurred on 8/28/07 had been scheduled to take place on 8/22/07. The schedule had been changed while the Supervisor was on leave on 8/22, 8/23 and 8/24/07. On 8/27/07 the testing was rescheduled and took place on 8/28/07. I explained that once the original results had been confirmed, the Field Alert should have been issued.

All retains of [REDACTED] have been tested during the course of this inspection with no other failing results. The investigation was not completed at the time of the close of the inspection (Exhibit 16).

There have been no complaints on Lot # 6048AQ.

**RECALL**



**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

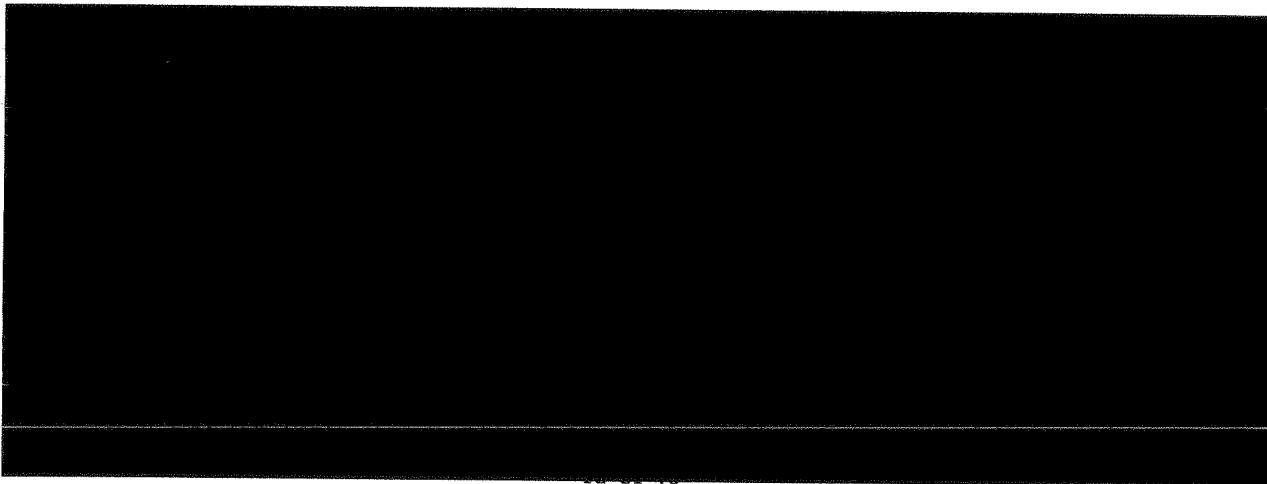
EI End: 09/28/2007

**MARKET WITHDRAWAL**

There was a market withdrawal on one lot of [REDACTED] Lot # 61000A1) due to a mislabeling of the product as Rx-only when this product is non-Rx. This discrepancy was brought to the attention of Actavis through a complaint on 12/28/06. The template was discovered to have been incorrect for this product only. The error occurred when the templates were changed for all labeling in order to change the name that appeared on the labeling from Amide to Actavis. This is the only lot of [REDACTED] distributed with the labeling error. The labeling group is located in Baltimore.

**BLEND UNIFORMITY**

Planned Deviation PD-07-006 was initiated on 1/17/07 in order to allow for the delivery of blend samples to the QC Laboratory as slugs. There was a high rate of blend uniformity failures due to this planned deviation. PD-07-006 called for all blends of 50 mg active or lesser concentration to be prepared as slugs and delivered to the laboratory for testing. Previously, there had been no issues with failure to meet blend uniformity specifications for any products. Investigations revealed that the failures were due to using thieves without the appropriate volume cavities and manipulating the slugs to create the correct weight of a sample for testing. There were additional manipulations of the samples in the way in which weights were measured through transferring the sample to the scale and then back into weigh paper envelopes, which were then taken to the lab. A Corrective and Preventive Action Request (CAPA) was opened on 3/19/07, which targeted the deficiencies noted above. New thieves and inserts were purchased in order to obtain the correct sample sizes and QA Samplers were trained to use pre-weighed glass vials in order to collect the samples instead of the previously used weigh paper envelopes.



**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FBI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

static charges from the sampling procedure. In addition, a CBE-30 has been submitted in order to change blend uniformity specifications to be in-line with content uniformity specifications with the use of an Acceptance Value in specifications instead of RSD.

**QUALITY SYSTEM**

The Quality System was evaluated during the current inspection. There have been many changes in personnel and in the quality systems since the previous inspection (Please see "Changes in Personnel and Operations" and "Voluntary Corrections" sections of this report for details.

Annual product reviews, complaints, deviations, investigations, change controls, rejected materials, stability failures, recalls, field alerts, quarantine products, process validations, computer validations, and training items were reviewed as part of the coverage to the Quality System.

Please see Observation #1 regarding Field Alerts.

**FACILITIES AND EQUIPMENT SYSTEM**

Coverage was provided for the Facilities and Equipment System. Equipment/Room Cleaning and Usage Logs, Equipment Calibration and Preventive Maintenance, Change Controls, Equipment Qualifications, Cleaning Validations, Recovery Studies, Detergent Studies, Equipment Identification Practices, and Pest Control Documentation were reviewed under this system.

**MATERIALS SYSTEM**

SOPs, receiving and warehousing procedures, FIFO, material inventory cards, storage conditions, location identification practices, storage under quarantine, sampling, release and rejection, and distribution procedures were reviewed as part of the coverage to the Materials System. A tour of the warehouse was provided and warehousing procedures were observed.

**PRODUCTION SYSTEM**

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

Coverage of the Production System included training, change control, deviations, investigations, batch record documentation practices, equipment identification practices, process validation, in-process sampling and testing, hold times, in-process and finished product specifications, adherence to batch manufacturing records, master batch records and equipment cleaning and use logs. A tour of Production was provided and manufacturing operations were observed including dispensing, blending, compression and encapsulation.

Please see FDA Observation #3 regarding the documentation of deviations.

**LABORATORY CONTROL SYSTEM**

The Quality Control Laboratory consists of 27 individuals, who are broken down into five teams: Finished Product and Stability, Raw Material/In-Process, Technical Services, Instrumentation/Metrology, and Laboratory Compliance. Major instruments include 25 HPLCs, 5 spectrophotometers, 8 dissolution baths, 3 particle size analyzers, 1 disintegration tester, 1 polarimeter, 2 autotitrators and 2 flurometers. The scheduling and documentation of calibration and preventive maintenance for all laboratory instruments is controlled by the CALMAN computer system. A tour of the Laboratory was provided, notebooks were reviewed for sample preparations and completeness, reagents and sample preparations as well as standards were appropriately identified throughout the laboratory. Up to date methods and specifications were available within the laboratory and raw data was reviewed both in notebooks and on the TotalChrom Data Acquisition System.

Please See FDA Observation #2 regarding the stability program.

**OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE**

Present for the closeout meeting were:

Scott Talbot, Site Head of Quality

Apurva Patel, Director, Site Operations

Phyllis Lambridis, VP, Quality Compliance for Actavis U.S.

Jasmine Shah, VP, Regulatory and Medical Affairs for Actavis, U.S.

**Establishment Inspection Report**

Actavis Totowa LLC  
Little Falls, NJ 07424-5608

FEI: 2244683  
EI Start: 09/05/2007  
EI End: 09/28/2007

Wanda Eng, Sr. Director Corporate Compliance for Actavis U.S.  
Garret Wolan, Compliance Manager for Actavis U.S.

**Observations listed on form FDA 483**

**QUALITY SYSTEM**

**OBSERVATION 1**

An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application.

Reference: 21 CFR 314.81(b)(1)(ii)

**Supporting Evidence and Relevance:**

The original flasks were reshaken and the results were similar (89.8 and 90.8), confirming the original results (Exhibit 8). Upon investigation, it was noticed that the blend used in this analysis was originally prepared on 8/6/07 and therefore it was determined that a new composite powder should be prepped and the analysis should be repeated. The results for this analysis were obtained on 8/21/07 and were 90.7 and 89.9, once again confirming the original results (Exhibit 9). A second analyst performed a repeat test on 8/28/07 with double the original sample prep and the results were 91.0, 92.6, 90.9, 92.3 (Exhibit 10). These were all in specification, but were low and therefore could not be used to disqualify the original results. Three additional bottles of this lot were pulled from stability and tested on 9/6/07 (Exhibit 11). These additional samples also gave failing results, Bottle 1: 86.4 and 88.5, Bottle 2: 88.2 and 87.9, Bottle 3: 90.9 and 89.0. The field alert was filed on 9/7/07 (Exhibit 12), which was in excess of three days of the original OOS results.

**Establishment Inspection Report**

Actavis Totowa LLC

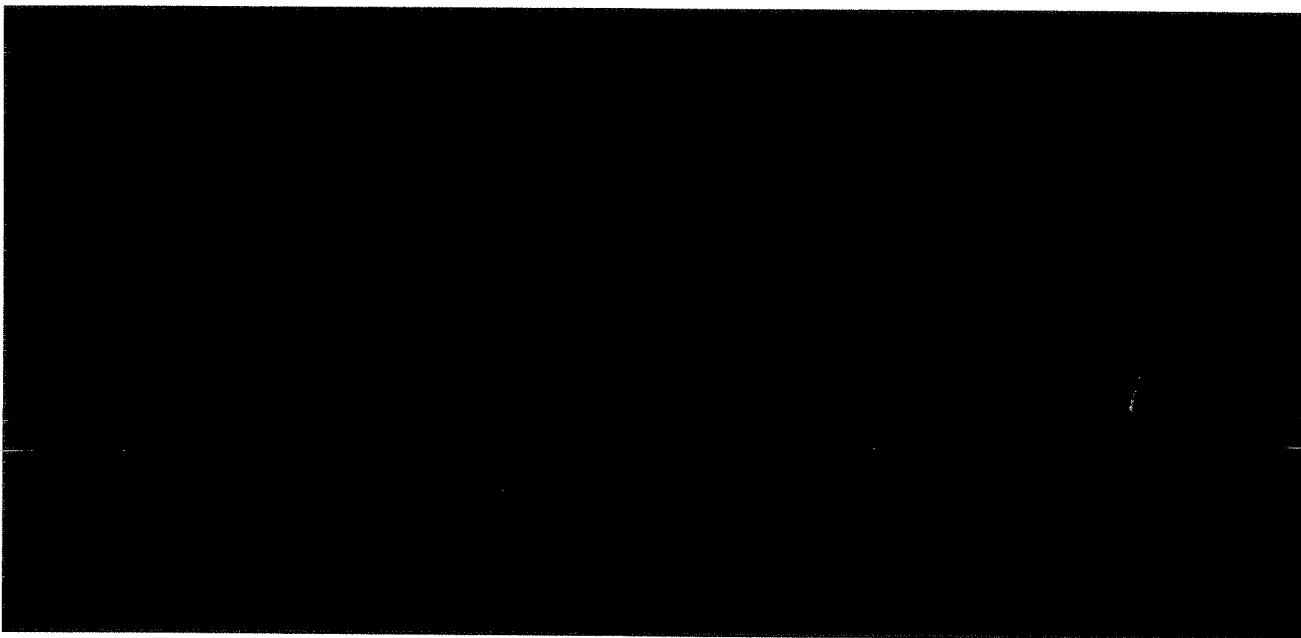
Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

I indicated that there were long gaps between the original testing on 8/21/07 and the repeat test performed on 8/28/07 and again between 8/28/07 and 9/7/07. Mr. Talbot explained that this was an error made in scheduling when the Laboratory Supervisor was on vacation. He indicated that the testing that actually occurred on 8/28/07 had been scheduled to take place on 8/22/07. The schedule had been changed while the Supervisor was on leave on 8/22, 8/23 and 8/24/07. On 8/27/07 the testing was rescheduled and took place on 8/28/07. I explained that once the original results had been confirmed, the Field Alert should have been issued.



There have been no complaints on Lot # 6048AQ.

All present at the closeout agreed with this Observation.

**LABORATORY CONTROL SYSTEM**

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**OBSERVATION 2**

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The written stability testing program is not followed.

Specifically, the following products were not tested at the 36-month stability test point:



**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

[REDACTED]

The above listed products were tested at a later date, but the cause for not conducting the testing at the appropriate time was due to incorrect assumptions that the product need not be tested due to changes in expiration dating.

Reference: 21 CFR 211.166(a)

Supporting Evidence and Relevance:

[REDACTED]

The above listed products were tested at a later date, but the cause for not conducting the testing at the appropriate time was due to incorrect assumptions that the product need not be tested due to changes in expiration dating. The stability coordinator mistakenly these products did not need to be tested because the product lines had changed expiration dating from 36 months to 24 months. However, these particular lots of product were manufactured under a 36 month expiry and therefore required testing. I indicated that one should not assume testing is unnecessary when products are due for testing.

All present at the closeout agreed with this Observation.

**PRODUCTION SYSTEM**

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**OBSERVATION 3**

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Written production and process control procedures are not followed in the execution of production and process control functions.

Specifically, the Standard Operating Procedures "Investigation of Deviations" (SOP # 0033) and "Investigation of Out of Specification Results" (DOI # QC-059) are not followed in that Investigations are not initiated when a deviation or out of specification result is detected and are not closed within 30 days. In addition, interim reports are not always written to document justification for investigations to remain open after each 30 day interval.

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

For example:

a) No investigation for Buspirone HCl Master Blend Lot 70683A was initiated as of 9/25/07 although the blend was placed on hold for unidentified particles discovered in the blend on 9/6/07.

b) Investigation of Deviation Reports 07-003 and 07-004 were issued on 1/19/07 and 1/29/07, respectively, but were not closed until 5/25/07.

c) Only one interim report was written for investigation 07-013, which was open from 3/14/07 through 7/21/07.

Reference: 21 CFR 211.100(b)

**Supporting Evidence and Relevance:**

Standard Operating Procedures "Investigation of Deviations" (SOP # 0033) (**Exhibit 22**) and "Investigation of Out of Specification Results" (DOI # QC-059) (**Exhibit 23**) are not followed in that Investigations are not initiated when a deviation or out of specification result is detected and are not closed within 30 days. In addition, interim reports are not always written to document justification for investigations to remain open after each 30 day interval.

A Hold Notification Form dated 9/6/07 indicated that [REDACTED] 0683A was placed on hold for unidentified particles discovered in the blend on 9/6/07 (**Exhibit 24**). No investigation was initiated for this blend as of 9/25/07. In addition, there was no notation in the batch record until I asked to see the batch record. The date of 9/25/07 was applied to the record on the date that I asked to see the batch record as an investigation had not yet been initiated (**Exhibit 25**).

An investigation for low yield of [REDACTED] 200/325/16mg, Lot 70488A was not initiated when the yield was determined to be 82.52% (specification = 90.0-100%) on 7/9/07. The batch record was signed off as reviewed and approved by production management prior to the initiation of the investigation on 7/18/07 (**Exhibit 26**).

Investigation of Deviation Reports 07-003 and 07-004 were issued on 1/19/07 and 1/29/07, respectively, but were not closed until 5/25/07 (**Exhibits 27 and 28**). I discussed the importance of concluding investigations and closing them out within reasonable timeframes.

Only one interim report was written for investigation 07-013, which was open from 3/14/07 through 7/21/07 (**Exhibit 29**). There should be justification provided in interim reports, to be written each 30 day period, in order to identify why an investigation remains open and what information may still be pending and why.

**Establishment Inspection Report**

Actavis Totowa LLC  
 Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

All present at the closeout meeting agreed with this Observation.

**REFUSALS**

There were no refusals throughout the course of this inspection.

**GENERAL DISCUSSION WITH MANAGEMENT**

The following items were discussed both during the inspection and again at the closeout meeting:

**-Cleaning within 30-day time frame**

During the tour of manufacturing, I identified one case in which Tablet Press #60 had not been cleaned before use after the 30-day time frame designated in SOP #0012 had been passed.

[REDACTED] had been compressed on this tablet press on 8/2/07.

The equipment had been cleaned on this date, but had not been cleaned again before the use of the equipment in the compression of [REDACTED] /07 although this time period between cleaning and the following use was in excess of 30 days. I did not observe any other instances in which equipment had not been cleaned when required.

**- Passwords**

During the second day of the inspection, a password was required to view the CMC section on the computer provided in the conference room. The individual logged on to the computer was not available and a second individual attempted to enter a password given to him over the phone in order to open the CMC section for my viewing. A discussion was held regarding the importance of password protection. I explained that although the only data available on the computer could not be manipulated in any way, it is not a good practice to share passwords of any kind.

**-Obsolete version of specifications available**

When I asked for the current specifications for [REDACTED] raw material, I was provided with revision 00, although the current Revision is actually 01. The Revision 00 of the specifications came from the QC Laboratory. I explained that no Revisions except the current Revision should be available unless it is clearly identified as obsolete. This situation will be remedied with the QMAS system.

**-Daily checks for balances**

The daily check made for balance #985 was observed to not bracket the usage range of the scale. It was noted that the external calibration does cover the entire usage range. I suggested at least covering the low and high points of the usage range during daily checks.

**-Inventory of bulk controlled on container labels**

**Establishment Inspection Report**

Actavis Totowa LLC  
 Little Falls, NJ 07424-5608

FEI: 2244683  
 EI Start: 09/05/2007  
 EI End: 09/28/2007

In reviewing the bulk inventory of [REDACTED] it was noted that the inventory is not controlled on the Batch Record Log as it is for packaged product. The deductions on the container labels did not include all deductions and the SOP "Batch Record Logs" (SOP #020) did not include instructions on how or where to document the inventory control of bulk product.

-Timeliness of investigations  
 [REDACTED]

During the coating of [REDACTED] lot # 60379A, the third coating pan of tablets was not of sufficient size to be coated appropriately according to the batch record. The MPR guideline for each pan load for barrier coating based on theoretical weight is 132.0 kgs  $\pm$  10kgs. The third pan load was 120.9 kgs (1.1 kgs below the lower limit). There was no planned deviation in order to allow this pan to continue the coating process. The product was rejected. I indicated that the yield specifications should be evaluated because this batch met yield specifications throughout production and there were still not enough tablets available to complete coating according to the MPR guideline.

Investigation 06-036 into the repeated complaints of broken [REDACTED] did not capture the fact that three of the six complaints referred to the same lot of [REDACTED] namely Lot # 5485A1. The investigation also indicated that no testing or retains was warranted, and there was no reference to investigating the type of container closure used in the packaging of each lot. Two packaging configurations may be used based on the customer; one is a 180cc round bottle and the other is a 160cc rectangular bottle. The possible need for additional cotton within the bottles was not explored and shipping conditions were not discussed. I explained that this investigation could have been more thorough.

-Procedure for Handling of Complaints

SOP: 34 Revision 6 does not include how to handle a complaint that comes from a customer for whom product is contract manufactured. I indicated that this should be included in the scope or the procedure should indicate if a separate system is being used to track complaints received from such customers.

-OOS # 07-007 [REDACTED] was not initiated within 24 hours. This OOS investigation was initiated nine days later. In addition this investigation was open from 1/19/07 through 5/24/07. More recent investigations have been initiated immediately and most have been closed within the designated timeframe.

-Cilostazol Tablets Process Validation Batch High Yield

The first of three process validation batches for [REDACTED] had a high yield of 103.19% after granulation. In investigation # 07-020, this high yield was attributed to moisture from production. The investigation did not determine any corrective action was necessary although the other two process validation batches exhibited yields of over 100% after granulation as well. I indicated that a corrective action does not have to be an immediate action, but can also consist of measures such as trending the next 5-10 batches produced in order to determine what an appropriate moisture specification or yield specification should be.

-Complaints

**Establishment Inspection Report**

Actavis Totowa LLC  
 Little Falls, NJ 07424-5608

FEI: 2244683  
 EI Start: 09/05/2007  
 EI End: 09/28/2007

A discussion was held regarding the timely handling of complaints. While some complaints were observed to take months to resolve with limited information as to why the complaints had not yet been closed, complaints received in recent months have been closed within 30 days.

**-Temperature Mapping of Drying Ovens**

In reviewing the heat distribution studies for the driers (which are expected to operate at 120 degrees F), it was noted that the acceptance criteria of  $\pm 15\%$  from the setpoint was designated as an acceptable tolerance for the read-out temperatures of the individual probes. I indicated that this meant that the chamber could range in temperature from 102-138 degrees. I explained that the tolerance should be tightened and noted that the actual results have been within approximately 2% of the setpoint. Mr. Talbot stated that the tolerance will be changed to  $\pm 5\%$  for all of the drying ovens.

**-Training**

In reviewing training records, it was noted that several employees did not receive initial GMP training until months after they were hired. For example one QA Inspector, hired on 3/19/07, did not receive GMP training until 7/13/07, whereas initial GMP training is to be given within the first week of employment. Mr. Vincent D'Esposito, QA Manager, Training has recently joined Actavis Totowa and is responsible for managing the training program, which includes GMP, SOP and OJT training. Recently hired individuals have received initial GMP training and the training program has been updated since Mr. D'Esposito began managing the training program.

**-TLC methods for Impurity Testing**

It was noted that the testing for impurities in [REDACTED] and [REDACTED] is conducted by HPLC. I indicated that this method would not reveal any unknown impurities and that it is not a stability indicating method. Production of this product has been discontinued.

**-Methods to be Validated prior to use on Submission Batch**

As indicated in a previous inspection, all methods should be validated prior to use on an ANDA submission batch. The methods for the testing of [REDACTED] were not validated until after the testing of submission batch RBR-2611. This batch was manufactured in 2006, prior to the change in the procedure indicating that submission batches will not be tested unless the method has been validated. The methods used in testing this batch are the same as those that are currently validated.

**SAMPLES COLLECTED**

Profile Sample # 377413 was collected at the close of this inspection.

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

**VOLUNTARY CORRECTIONS**

Corrections to the previous FDA 483 were reviewed with Ms. Wanda Eng, Sr. Director Corporate Compliance for Actavis U.S. The previous 483 Observations and the associated corrections appear below.

**OBSERVATION 1**

The quality control unit lacks authority to fully investigate errors that have occurred.

Specifically, there is no assurance that the Quality Unit can be relied upon to fulfill its responsibilities to assure that all drug products released to the marketplace meet the requirements for identity, strength, quality, and purity that they purport to have. Batches of drug products that initially failed to meet release specifications were released into interstate commerce without being fully investigated, all laboratory data was not included with the batch records and manufacturing deviations were not always documented.

**Corrections:**

A number of individuals have been hired and/or have been promoted since the previous inspection, including, but not limited to:

Phylis Lambridis, Vice President of Quality and Compliance, U.S.

Scott Talbot, Site Head of Quality

Paul Galea, Director of Quality Systems

Vince D'Esposito, Training Manager

Swapan Roychowdhury, Director, Quality Control

Jisheng Zhu, Quality Control Manager

Elina Novikov, Stability Manager

Chrystal Day, Stability Coordinator

Joaquin Mejia, Stability Coordinator

Bernard Glover, CAPA and Complaints Specialist

Mike Ponzo, Investigation Specialist

Tony Castallezzo, Director, Quality Assurance, Totowa (located in Riverview facility)

Elizabeth Guarch, Validation Manager

Irina Kotkova, Validation Specialist

Lauren Miranda, Quality specialist

Pam Barckett, Documentation Specialist

In addition, four new analysts and two temps have been brought into the QC Laboratory. An additional two analysts were hired during the course of the inspection.

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

Since the previous inspection, the number of individuals in the Quality Assurance Department has increased from 13 to 27. This is equivalent to a change in the ratio of Operation/Quality personnel from 3.5 to 2.8.

All Standard Operating Procedures (SOPs) and Departmental Operating Instructions (DOIs) have been reviewed and uploaded into QMAS, a validated computer system, which will enable employees to access all procedures and instructions on-line and will ensure that only the most current revision of each SOP and DOI is available for reference. Laboratory methods are currently being entered into the QMAS system for the same purpose.

Calibration Manager (CALMAN) was validated in the end of 2006. This program has been fully operational since March 2007 and is used for the scheduling and documenting of calibration and preventative maintenance operations in both the laboratory and manufacturing.

Microcontrol Solutions Stability System II has been implemented in order to manage the stability program. The software generates pull schedules and is used for storing all information related to the stability program.

Trackwise is to be utilized in the future in order to document and track Deviations, Investigations, Change Controls, Out of Specification Investigations. The roll-out of this program is anticipated to be by the end of 2007.

Consultants were hired and retained over the last year to perform a number of functions. They were utilized in the re-training of Laboratory and Quality Assurance personnel in the areas of Deviations, GMPs and Good Documentation Practices, as well as additional refresher trainings. All process validations were evaluated for accuracy and completeness and all equipment qualifications for production and laboratory equipment/instruments were reviewed. For all products on the market since the previous inspection through Feb 2007 that were associated with any type of deviation or investigation, consultants reviewed all associated Deviations, QA Investigations, OOS Investigations, and Batch records. In addition, a representative sample of batches manufactured was also selected for full review. The review of this representative sample should be completed in the near future.

The Quality Systems Improvement Plan (QSIP) was initiated as of August 29, 2006. QSIP was organized into 17 sections, including Organization, Management Review, Laboratory Controls, Micro/Environmental Monitoring, Investigations, CAPA, Documentation, Change Control, Validation, Training, Incoming Materials, Finished Product Release, Compliance/Audits, Warehouse/Distribution, Facilities and Equipment, Manufacturing Technology Transfer and Computer Validation. A copy of the plan was provided and is attached as **Exhibit 6**. Actavis has been updating Compliance Branch regularly regarding the status of their progress in QSIP. Progress was reviewed during the current inspection and many positive changes have been made since the previous inspection due to the implementation of this program.

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

For additional corrective actions please see each following Observation.

**OBSERVATION 2**

Laboratory records are deficient in that they do not include a complete record of all data obtained during testing.

Specifically, the Quality Unit failed to assure that laboratory notebooks include all data generated during testing and that analysts document in their laboratory notebook all sample preparation and testing at the time it occurs. Additionally, SOP QC-59 Investigation of out of specification test Results (OOS) is not always followed. For example:

- a) On 1/11/06, during content uniformity testing of [REDACTED] the analyst noticed that the first two capsules were out of specification and he aborted the run. The audit trail for the laboratory data acquisition system does not indicate that the run was aborted and the analyst did not print the sample results or report the failing results in the laboratory notebook. An investigation was initiated and it concluded that a sample dilution error was made. A review of the lab notebook shows the sample dilution value in the laboratory notebook was over written, without being signed and dated as required. Additionally, a review of the laboratory notebook page showing the sample preparation and a photocopy of the same page in the investigation report, revealed that they were not the same. Changes were made in the laboratory notebook after it was signed and approved.
- b) The original result of 66.5% for Sample 1-1 for pooled dissolution of [REDACTED] was not documented in Laboratory Notebook # 700-34 and was not attached to the hard copy chromatograms. An additional injection was made for Sample 1-1 within the same chromatographic run and was used in the calculations. The original result had not been invalidated.
- c) The original result of 77.7% for Capsule-2 dissolution sample for [REDACTED] was not documented in Laboratory Notebook # 349-08. An additional injection was made for Capsule-2 within the same chromatographic run and was used in the calculations. The original result had not been invalidated.
- d) [REDACTED] was tested on 5/31/06 and failed to meet the specification for impurities. A new sample preparation was prepared and the batch was retested within the same chromatographic run, without prior approval as required. The original results and the results of the new sample preparation appear together in the laboratory notebook not one after the other. The out of specification (OOS) results for high impurities were invalidated without any scientific justification and the batch was retested and released. This same batch had a low yield due which was attributed to compression problems. The entire batch was compressed below the action limit for hardness, which resulted in the rejection of approximately 50,220 broken tablets, or 4.25 % of the batch.
- e) The original result of 89.9% for Assay-1 in the analysis of [REDACTED] 4 month stability was not documented in Laboratory Notebook # 666-01. An additional injection was made for Assay-1 within the same chromatographic run and was used in the calculations. The original result had not been invalidated.
- f) There was no notation in Laboratory Notebook # 349-07 although the original result for Assay-1 of Amidrine Capsules Batch # 5113A did not show any peaks (due to injection of the wrong vial). An additional injection was made and results were recorded without documenting the discrepancy. A note was later squeezed into the Laboratory Notebook just above the "Conclusion" section of the analysis.
- g) On 10/7/05 during the testing of [REDACTED] one assay value was approximately double the expected value. The failing results were attributed to a transcription error in the

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

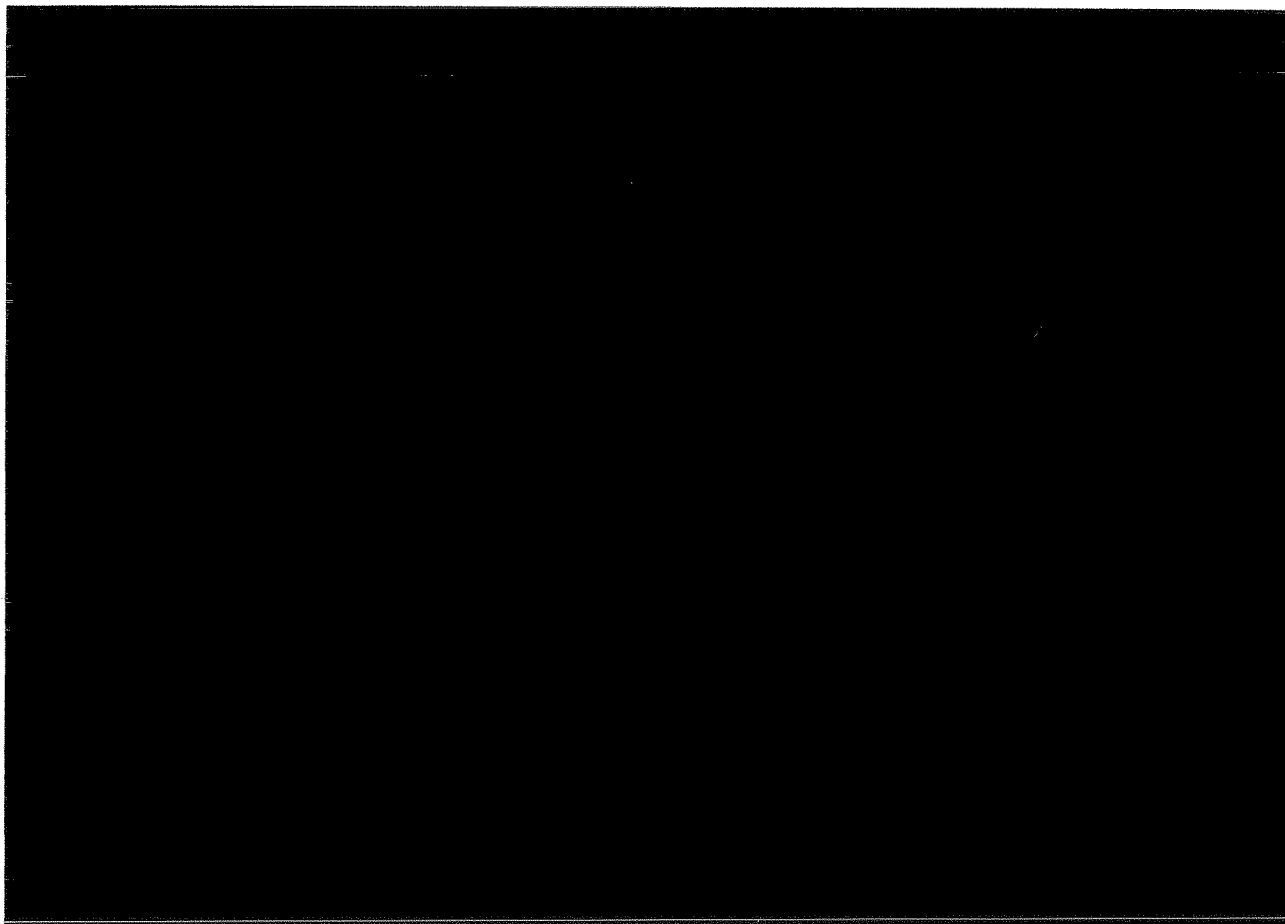
sample weight. The failing results were not recorded in the laboratory notebook and were not printed from the laboratory data acquisition system.

**Corrections:**

All analysts have been retrained since the previous inspection and have had specific training on documentation practices as well as additional training on how to conduct adequate deviation investigations. Any changes to a chromatographic sequence now require supervisory approval. New procedures have been put into place in order to ensure that all data is documented within laboratory notebooks. These procedures include: QC 002: Laboratory Notebook and Review Procedures and QC 106: Evaluation of Laboratory Error. In addition DOI QC 059 was revised to state "If the error is observed after sample measurement began, the analysis should be carried out to the end without interruption".

**OBSERVATION 3**

The responsibilities and procedures applicable to the quality control unit are not fully followed.



**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

0079. Step 5.3.2.2 of Procedure SOP 0055: Process Validations, effective 9/6/07 states to justify and discuss deviations in validation reports. A current process validation report was reviewed which did discuss a failure to meet yield specifications. In addition, QC 059: Investigation of OOS and Suspect test results has also been updated.

A QA coordinator has been hired to manage change controls. SOP 0065: Change Control has been updated.

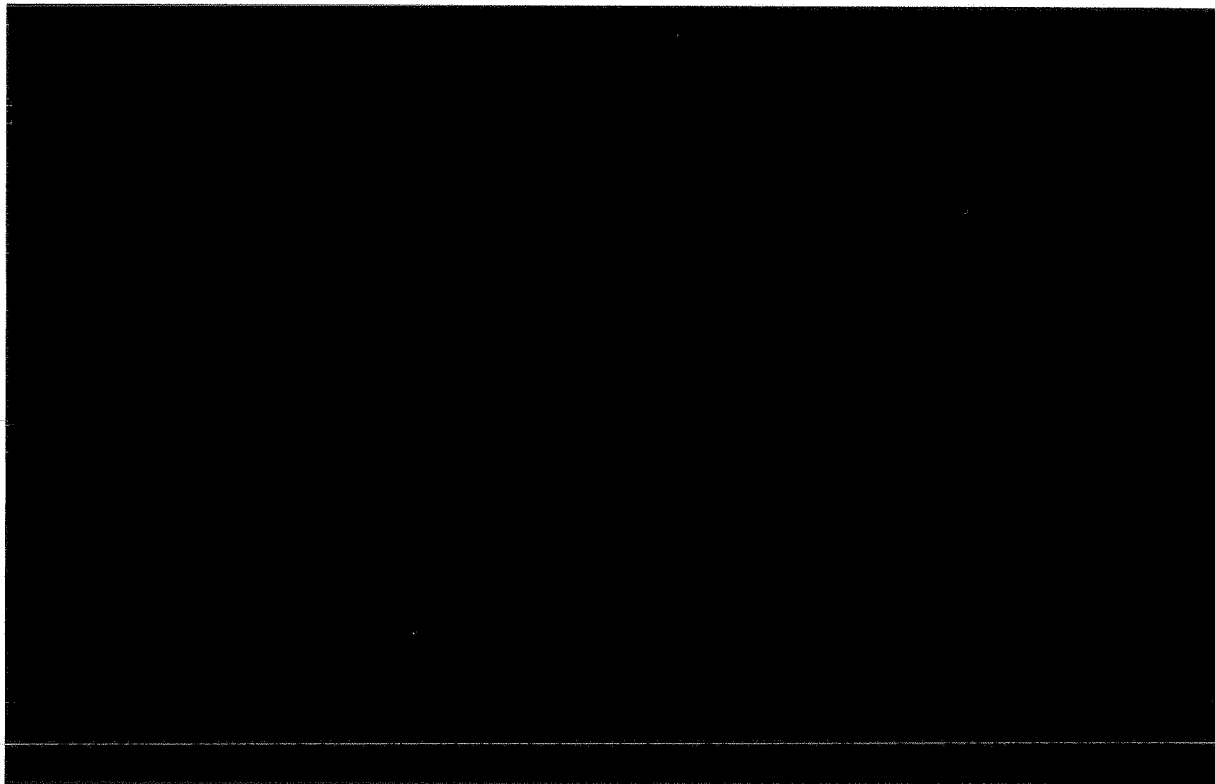
A letter was sent to CDER to correct the exhibit batch number for Benzotropin Mesylate that was filed in the ANDA.

**LABORATORY CONTROL SYSTEM**

**OBSERVATION 4**

Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications.

Specifically, investigations were not conducted when out of specification (OOS) results were generated. Samples were retested and the original results were not invalidated. For example:



23-0140

**Establishment Inspection Report**

Actavis Totowa LLC  
Little Falls, NJ 07424-5608

FEI: 2244683  
EI Start: 09/05/2007  
EI End: 09/28/2007

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until 7/19/05.

**Corrections:**

All data generated will be documented in laboratory notebooks and the firm has updated the OOS procedure QC-059: Investigation of Out-Of-Specification and Suspect Test Results, was updated to require all analysts to run all chromatographic testing to completion unless an error is detected before a sample is run. SOP 0033: Investigation of Deviations was updated. All analysts have been retrained.

3<sup>rd</sup> party consultants have reviewed all deviation investigations for both laboratory and manufacturing.

Audit trails are reviewed and all raw data is printed.

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**OBSERVATION 5**

Input to and output from the computer are not checked for accuracy.

Specifically, audits were not conducted of the TotalChrom Data Acquisition System used to run the HPLC instruments during analysis of drug products. Sample injections, processing methods, and sample weights were not reviewed or verified for the accuracy of reported sample results during testing of in-process, finished product and stability samples.

**Corrections:**

New procedures are in place in order to conduct audits of the TotalChrom Data Acquisition System, which is used to run the HPLC instruments. The Graphic Edit Mode function has been disabled in order to ensure accuracy of the laboratory data. DOI QC 155a: Using TotalChrom Client Server Software for Analysis was written to ensure that weights of standards and purity of actives are checked. DOI QC 155p: Procedures to Assign a File Name for TotalChrom Client/Server Data Acquisition was put in place in order to designate a system of assigning file names. DOI QC 155q was written as a procedure to review the accuracy of the data generated by TotalChrom and the audit trail in the Method Sequence file.

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**OBSERVATION 6**

The suitability of all testing methods is not verified under actual conditions of use.

Specifically, there is no assurance that equipment is adequately cleaned due to the deficiencies in cleaning validation studies. For example:

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

a)

mg. Digoxin Tablets USP 0.25 mg.

b)

c)

d)

**Corrections:**

Recovery studies were performed on 33 products in a manner in which APIs were spiked onto a coupon, swabbed and then analyzed for recovery. A cleaning validation and recovery study were reviewed during the current inspection in order to verify this corrective action. The SOP for Cleaning Validation has been revised and all cleaning validations are to be included in a matrix approach, the protocol for which has been approved as of 6/27/07. The matrix includes hardest to clean and most potent drug products. Detergent studies were completed on the cleaning agent used. The following procedures have been updated: DOI PRD 002: Room Usage and Cleaning Log, SOP 0012: Production Department Cleaning Procedures, DOI PRD 095: Cleaning Agents used in the Production Areas and DOI PRD 001: Equipment Usage and Cleaning Log.

**OBSERVATION 7**

The written stability testing program is not followed.

Specifically, the stability data recorded as that of bulk stability hold time studies are actually obtained from the testing of the following packaged finished products:

[REDACTED]

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

Imipramine Hydrochloride Tablets, USP 10 mg, 25 mg, 50 mg

Methimazole Tablets, USP 5 mg, 10 mg

Phendimetrazine Tartrate Tablets, USP 35 mg

**Corrections:**

At the conclusion of the previous inspection, Mr. Shah explained that the "Stage" Field had been updated such that the Data Processor may now enter "Bulk Tablets" instead of "Finished Product" so that there is no confusion when the Quality Assurance Packaging Supervisor is pulling samples to submit to the laboratory. All of the bulk hold time studies have been repeated on each of the above listed products at time points beyond three months as an immediate corrective action.

Corrections to the stability program have been verified during the current inspection. SOPs and DOIs were updated in order to prevent this situation from reoccurring. The following procedures were revised: SOP0025: Stability Program, DOI: QC 166: Modification to Stability System Software, DOI: QC 167: Logging in and Managing Data using Stability Software System, DOI: QC-041: Stability Chamber Monitoring.

During the inspection, I spoke with Elina Novikov, QC Laboratory Compliance Manager about the new Microcontrol Solutions Stability System II, which has been implemented in order to manage the stability program. She explained that the software generates pull schedules and is used for storing all information related to the stability program. She indicated the program can track schedules, identify trends, store data, indicate when the next test station is due, record date of pull, who pulled the sample, when testing is initiated and when completed. She indicated that older stability data for lots still on the market is currently being added to the computer system. She estimated that all data should be entered by the end of June or July 2008. Ms. Novikov explained that pull dates will no longer be missed according to this corrective action.

**PRODUCTION SYSTEM****OBSERVATION 8**

Examination and testing of samples is not done to assure that in-process materials conform to specifications.

Specifically, on numerous occasions quality assurance personnel failed to detect tablets and capsules which did not meet in-process specifications for tablet weight and thickness. SOP-016, "Routine Tablet Press Overcheck", requires a new set of samples be taken when out of specifications results are encountered, this did not occur. For example:



**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

b)

c)

d)

e)

*Please note: There was a typographical error in issuing 483 where Observation 8d and 8e were combined.*

**Corrections:**

A retraining was held for QA personnel (those who perform in-process checks) prior to the close of the previous inspection. An additional inspector was added to the QA manufacturing Inspector Group. DOI QA 016: Routine Tablet Press Overcheck was revised in order to notify supervisor if thickness or hardness do not meet specifications.

**OBSERVATION 9**

Deviations from written production and process control procedures are not recorded and justified.

Specifically, there is no assurance that all manufacturing deviations are documented. For example:

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FBI:

2244683

EI Start:

09/05/2007

EI End:

09/28/2007

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c)

**Corrections:**

All operators were retrained. DOI PRD-122: Batch Record Data Entry was updated to require that non-routine occurrences or out of specification results be properly documented. DOI PRD 084: Tablet Press Operation, DOI PRD 169: Bosch & Bohanan 2000 Encapsulation Machine, Operation and DOI PRD 232: SeJong SSF 100N Encapsulation Machine Operation was also updated to include "If the tablets/capsules are out of specification, stop the tablet press/encapsulation machine and immediately notify Production and Quality Assurance.

**OBSERVATION 10**

The master production and control records are deficient in that they do not include complete sampling and procedures.

There is no assurance that all in-process blend samples collected from the mixer are 1 x 3 times the tablet/capsule weight as required. The sample collection is not documented and the sample weight is not measured. For example:

The QA submission form, which is submitted to the laboratory with the in-process blend uniformity samples, does not include the sample weights and the collection of the samples is not recorded in the Batch record.

**Corrections:**

Sample submission forms were revised to include individual sample weights for each of the blend sample locations. These documents have been implemented. Documentation of sample weights is now performed with a target of 2 X dose, and 1 to 3 X is acceptable. The following procedures have been updated: QA 012: Sampling Instructions for Double Cone Blenders, SOP 0031: In-Process and Finished Dosage Testing and DOI QA 043: Sampling Instructions for Twin Shell Blenders.

## Establishment Inspection Report

FEI: 2244683

Actavis Totowa LLC

EI Start: 09/05/2007

Little Falls, NJ 07424-5608

EI End: 09/28/2007

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FACILITIES & EQUIPMENT SYSTEM

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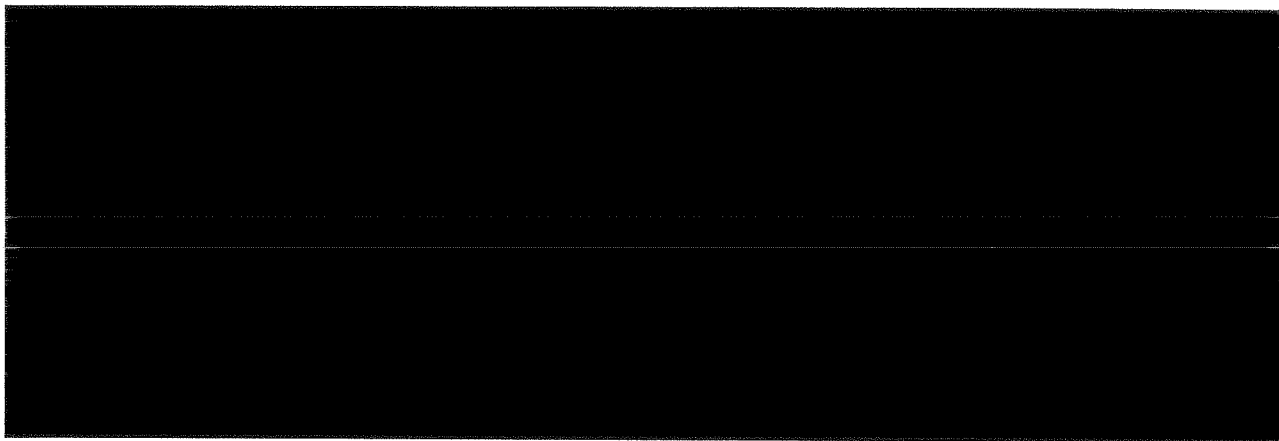
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OBSERVATION 11

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Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically, equipment qualifications are deficient in that acceptance criteria are not specified, and discrepancies are not documented. For example:



## Corrections:

All manufacturing and laboratory equipment/instruments have been reviewed for qualification. All equipment/instruments have been qualified. Review and remediation was conducted by third party consultants. The Stokes BB2 Tablet Press, equipment # 70 and 71 were assessed by Aronson and Kaufman Associates. The Lydon Brothers Inc. Drying Oven ID # 271 and the Blue M Drying Oven ID # 273 have been qualified.

In reviewing the heat distribution studies for the driers (which are expected to operate at 120 degrees F), it was noted that the acceptance criteria of  $\pm 15\%$  from the setpoint was designated as an acceptable tolerance for the read-out temperatures of the individual probes. I indicated that this meant that the chamber could range in temperature from 102-138 degrees. I explained that the tolerance should be tightened and noted that the actual results have been within approximately 2% of the setpoint. Mr. Talbot stated that the tolerance will be changed to  $\pm 5\%$  for all of the drying ovens.

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

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**OBSERVATION 12**

Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically, there is no assurance that preventative maintenance is conducted for equipment at scheduled intervals. For example:

- a) Duct tape was observed on the feed throat of Fitzmill #12 during the tour of manufacturing operations.
- b) There are no preventative maintenance programs for the Lydon Brothers Inc. Drying Oven ID # 271 or the Blue M Drying Oven ID # 273.
- c) Preventative Maintenance is to be conducted on Double Cone Blender ID # 41 every six months according to DOI # PRD-011: Blenders - Preventative Maintenance and Repairs." However, no maintenance had been conducted between 1/8/04 and 12/8/04 or between 5/12/05 and 5/19/06.

**Corrections:**

SOPs DOI 248: Drying Oven calibration, DOI 249: Drying Oven Preventative Maintenance and Repairs and DOI PRD 011: Blenders – Preventive Maintenance & Repairs provide procedures for preventative maintenance for the drying ovens and blenders. The duct tape was removed from the feed throat of the Fitzmill and is no longer used on any equipment. A maintenance mechanic has also been hired since the previous inspection.

In addition, the Calibration Manager computer system has been validated. This program has been fully operational since March 2007 and is used for the scheduling and documenting of calibration and preventative maintenance operations in both the laboratory and manufacturing.

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**MATERIALS SYSTEM**

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**OBSERVATION 13**

Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacturing or processing operations for which they are unsuitable.

Specifically, rejected Batches are not labeled as rejected or placed in a section of the warehouse for rejected products. For example:



**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

b)

c)

**Corrections:**

Departmental Operating Instructions, DOI QA 002: Rejecting an Item, was updated to include timeframes for hold/rejection status and for placing the rejected stickers on the product. In addition, DOI PRD 255: Reject Cage Operations to include directions on how to handle rejected materials.

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**OBSERVATION 14**

Written procedures are not followed for the receipt and storage of components.

Specifically, all locations are not identified throughout the warehouse as required by Departmental Operating Instructions (DOI) PRD-068: "Raw Material Locator System", nor are they recorded on Material Inventory Cards as required by DOI PRD-066: "Receiving Raw Materials & Packaging Components," to describe where materials are located in the warehouse. For example:

a)

b)

**Corrections:**

All locations within the warehouse have been identified and locations are now recorded on the Material Inventory Cards. Retraining was given to operators regarding the revised SOPs: DOI WHS 001: Receiving Raw Materials and Packaging Components, DOI WHS 003: Raw Material Locator System and DOI WHS 005: Material Inventory Card.

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**OBSERVATION 15**

There was a failure to handle and store components at all times in a manner to prevent contamination.

Specifically, all raw materials for a Batch are weighed in the manufacturing room without cleaning between the dispensing of each ingredient. The cleaning log for the room only reflects the cleaning of the room after the production

**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI: 2244683

EI Start: 09/05/2007

EI End: 09/28/2007

of the Batch. In addition, procedures do not indicate that the active ingredient should be the last material to be weighed.

**Corrections:**

DOI PRD247: Operating Instructions for Weighing Raw Materials to be Used in Pharmaceutical Production, was updated in order to state that inactive ingredients are to be weighed first, one at a time, active ingredients are to be weighed last and a dry cleaning is to take place between the dispensing of each ingredient. In addition, the new facility on 900 Riverview Drive, Totowa, NJ has specifically designated dispensing rooms for future production operations.

The following discussion item from the previous inspection was also verified as corrected during the current inspection.

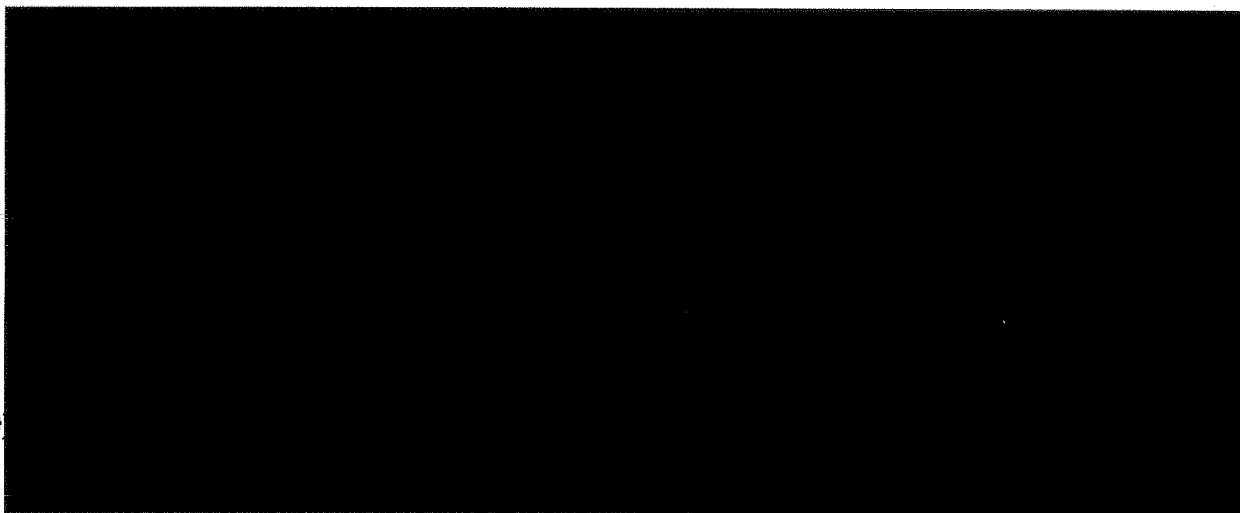
***Labeling of glassware:***

During the tour of the analytical laboratory, I noted that all glassware on bench tops were clearly labeled and identified according to DOI: QC-157: Labeling of Standard/Sample Solution Vessels. This procedure had been presented prior to the close of the previous inspection.

An outline of corrective actions taken in response to the previous FDA 483 was provided by Ms. Wanda Eng and is attached as **Exhibit 30**.

**EXHIBITS COLLECTED**

- 1)
- 2)
- 3)
- 4)
- 5)
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- 8)
- 9)
- 10)



**Establishment Inspection Report**

Actavis Totowa LLC

Little Falls, NJ 07424-5608

FEI:

2244683

EI Start:

09/05/2007

EI End:

09/28/2007

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**ATTACHMENTS**

FDA 482, dated 9/5/07, 1 page

FDA 483, dated 9/28/07, 3 pages

**Establishment Inspection Report**

FEI:

2244683

Actavis Totowa LLC

EI Start:

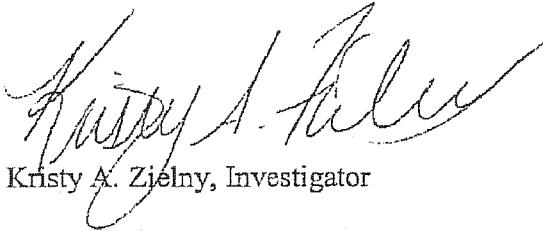
09/05/2007

Little Falls, NJ 07424-5608

EI End:

09/28/2007

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Kristy A. Zielny, Investigator